REMARKS

ANTICIPATION REJECTION - MEHRA ET AL.

Claims 1-6, 10, 11, 17, and 25 stand rejected under 35 U.S.C. § 102(b) as anticipated by Mehra et al. (USPN 65,830,576). This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). To be prior art under 35 U.S.C. § 102, the reference must put the anticipating subject mater into the possession of the public through an enabling disclosure. *Chester v. Miller*, 906 F.2d 1574 (Fed. Cir. 1990).

As recited in independent claim 1, the present invention relates to a method for selecting an optimized controlled release dosage form for administration to a patient such that the dosage form will have a predetermined drug release profile *in vivo*, the method comprising (a) preparing a plurality of different candidate dosage forms each comprised of a biocompatible, hydrophilic polymer and a pharmacologically active agent incorporated therein; (b) obtaining the *in vitro* drug release profile for each candidate dosage form in an aqueous medium in a USP disintegration tester; (c) comparing the *in vitro* drug release profiles obtained in (b), and determining which of the *in vitro* drug release profiles correlates most closely with a desired *in vivo* drug release profile; and (d) selecting the dosage form having the determined *in vitro* drug release profile for administration to a patient.

As recited in independent claim 17, the present invention also relates to a method for delivering a pharmacologically active agent to the upper gastrointestinal tract of a patient over an extended period of time while minimizing delivery to the lower gastrointestinal tract and colon, the method comprising orally administering to a patient in whom the fed mode has been induced a sustained release oral dosage form comprised of a therapeutically effective amount of the pharmacologically active agent incorporated in a matrix of at least one biocompatible, hydrophilic polymer that (a) swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide gastric retention of the dosage form in the stomach of a patient in whom the fed mode has been induced; (b) gradually erodes within the gastrointestinal tract over a determinable time period; and (c) releases the active agent throughout the determinable time period, wherein the dosage form is optimized by subjecting the dosage form to a disintegration test for an extended period of time such that the dosage form has an *in vitro* active agent release profile that correlates to a desired *in vivo* active agent release profile for the dosage form.

Mehra et al. teaches herbicide tablets made with at least one nitrogen compound (i.e., urea or an ammonium sulfate or phosphate) and microcrystalline cellulose alone or in combination with a

suspending agent. The compositions are formulated via dry or wet granulation to form tablets that disintegrate rapidly in an aqueous solution.

The Examiner is citing Mehra et al. for the disclosure of celluloses to manufacture solid dosage forms (the Examiner cites col. 3, ll. 48-42 and Example 9) and the use of the USP disintegration test to determine the disintegration of the granules in the solid dosage form (the Examiner cites col. 8, ll. 13-20). The following discussion will demonstrate why the teachings of Mehra et al. do not anticipate the claimed invention.

At page 2, item 3, the Examiner asserts that Mehra et al. discloses a diuretic formulation; however, nowhere in Mehra et al. is a diuretic mentioned. While urea is a known diuretic, Mehra et al. is very clear that the urea for the dosage form disclosed therein is used as a nitrogenous pesticide for agricultural purposes. At the top of page 3, the Examiner asserts that the dosage form of Mehra et al. is administered; however, Mehra et al. has no teaching of the administration of the dosage form disclosed therein to a human. While Mehra et al. briefly mentions that the dosage form may be used to deliver active agents to body fluids (col. 4, line 40), Mehra et al. provides no teaching that would lead the ordinary artisan to modify the dosage form described therein, which is enabled only for an agricultural pesticide, for administration to a human. On this matter, applicants must emphasize that it is a well-established principle of patent law that for a reference to be properly applied under 35 U.S.C. § 102, it *must be enabling*. *See, Chester v. Miller, supra*. Applicants submit that Mehra et al. is *not* enabling for the administration of the dosage forms disclosed therein to a patient, such as the human patient contemplated under the present invention.

Notwithstanding the foregoing, applicants would like to emphasize that the use of a disintegration test for the optimization of a controlled-release dosage form for administration to a patient is significantly different from the use of a disintegration test for the optimization of a rapidly disintegrating dosage form for delivering a pesticide (Mehra et al. expressly teaches that the dosage form is an immediate release dosage form; *see, e.g.*, col. 1, ll. 10-13, 22-25, and 33-37). As a preliminary matter, applicants must emphasize that except for immediate release dosage forms, disintegration testing is not used in the pharmacological arts for the optimization of controlled release dosage forms because in the 1960s and 1970s, disintegration testing was found to have little relevance to the *in vivo* performance of the controlled release dosage forms. *See, e.g.*, J.G. Wagner, BIOPHARMACEUTICS AND RELEVANT PHARMACOKINETICS, Ch. 15, Drug Intelligence Publications, Hamilton, IL (1971) (attached to the end of this paper). When considering that disintegration testing is premised on the time for rupture of a dosage form while dissolution testing is premised on the rate at which a dosage form dissolves, it follows logically that disintegration testing would be useful for optimizing the active agent release profile of

immediate release dosage forms while dissolution testing would be useful for optimizing the active agent release profile of controlled release dosage forms.

Thus, in direct contravention to the state of the art, the present invention unexpectedly and surprisingly, uses the disintegration test to determine the active agent release profile of the claimed controlled release dosage form, rather than a dissolution test. Directing the Examiner's attention to Example 1, there, an experiment is conducted to determine whether a dissolution test or a disintegration test provide a better correlation to *in vivo* drug release of topiramate, a sparingly soluble drug. The results of the tests are shown in Figure 1. At paragraph 0152 it is explained that the Polyox N-80 used to formulate the matrix particles in the tablet (*see*, paragraph 0149) act more like a disintegrant than a binder. This surprising and unique feature of the controlled release dosage form of the present invention resulted in the disintegration test being a more accurate tool in predicting *in vivo* erosion of matrix systems than the dissolution test (*see*, paragraph 0153). Figure 2 clearly shows that for the dosage form of the present invention, the disintegration test provides a closer correlation to *in vivo* release than does the dissolution test (*see also*, paragraph 0154).

The foregoing discussion demonstrates that one of the unique and surprising features of the claimed invention is that the claimed dosage form displays an *in vivo* drug release profile that correlates to the *in vitro* active agent release profile of the dosage form in a disintegration test rather than a dissolution test. Because Mehra et al. does not teach or suggest that the dosage form disclosed therein may be optimized for administration to a patient by using a disintegration test to correlate the *in vitro* and *in vivo* active agent release profiles, it follows that Mehra et al. does not anticipate or render obvious the claimed invention. For the foregoing reasons, applicants respectfully request withdrawal of this rejection.

ANTICIPATION REJECTION - FRANZ ET AL.

Claims 1-8, 10-13, 17, 18, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Franz et al. (USPN 5,232,704). This rejection is respectfully traversed.

Franz et al. teaches a sustained release pharmaceutical dosage form that is formulated in a capsule. The dosage form is an uncompressed bilayer formulation with one layer comprising a drug release layer and the other layer comprising a buoyant or floating layer, the latter providing buoyancy to the dosage form and diametral increase (Abstract; col. 4, ll. 16-19).

The Examiner cites col. 9, lines 7-30, for the teaching of the use of the USP disintegration test and col. 12, lines 25-50, for the teaching of *in vivo* studies. The following discussion will demonstrate why these teachings of Franz et al. do not anticipate the claimed invention.

First, applicants would like to emphasize that the reference in Franz et al. to the disintegration test at col. 9, lines 7-30, does not teach or suggest that the disintegration test is being used to test the *in vitro* drug release profile of the active agent in the dosage form; rather, there, Franz et al. is using the disintegration test solely to determine the durability and stability of the drug release layer. Indeed, the disclosure at col. 9, lines 7-30, of Franz et al. does not discuss how much active agent was released during erosion using the disintegration test; it merely discusses the use of the disintegration test to test the stability and durability of the dosage form.

Second, directing the Examiner's attention to col. 21, lines 32-56, of Franz et al., there Franz et al. is clearly using a dissolution test to determine the release profile of the active agent from the sustained release dosage form; Franz et al.'s use of the dissolution test in this manner is in complete accordance with the accepted practices in the art at the time of the Franz et al. patent and also prior to the present invention (*see*, the discussion in the traversal to the Mehra et al. rejection).

Because Franz et al. does not teach or suggest that the disintegration test is used to correlate the *in vitro* and *in vivo* drug release profiles of the active agent from the sustained release dosage form disclosed therein, it follows that Franz et al. does not anticipate or render obvious the claimed invention. For the foregoing reasons, applicants respectfully request withdrawal of this rejection.

OBVIOUSNESS REJECTION - SHELL ET AL. IN VIEW OF TEACHINGS IN THE SPECIFICATION

Claims 1-26 stand rejected under 35 U.S.C. § 103(a) as obvious over Shell et al. (USPN 5,972,389) in view of the teachings in the specification. This rejection is respectfully traversed.

When establishing a *prima facie* case of obviousness, the Office must show that the cited prior art references, either singly or in combination, suggest the desirability of the claimed subject matter. *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986). That the inventor achieved the claimed invention by doing what those skilled in the art suggested should not be done is a fact strongly probative of nonobviousness. *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 230 USPQ 81 (Fed. Cir. 1986), *on rehearing*, 231 USPQ 160 (Fed. Cir. 1986).

Shell et al. teaches a gastric retentive oral dosage form that is tested with USP dissolution test equipment. At page 4 of the Office Action, the Examiner acknowledges that Shell et al. does not disclose testing disintegration of the dosage form. The Examiner is of the opinion, however, that the disclosure at paragraph 0005 of the specification that disintegration test data is used to supplement dissolution test data to predict *in vivo* drug release profiles renders the claimed invention obvious in view of Shell et al. In the latter half of the paragraph at the top of page 4, the Examiner requests a showing that the disintegration test is unexpectedly superior to the dissolution test for predicting *in vivo* drug release.

In response, applicants must emphasize that the reference to conventional disintegration testing in paragraph 0005 of the specification is in specific reference to *immediate release dosage forms*. There, it is expressly stated that the disintegration test described in USP 24-NF 19 § 701 is *not* to be used for modified release dosage forms; the claimed invention is a controlled release dosage form, *not* an immediate release dosage form. Thus, contrary to the Examiner's assertion, paragraph 0005 of the specification actually teaches that according to the state of the art at the time of the invention, dissolution testing, and *not* disintegration testing, was used for testing active agent release profiles in controlled release dosage forms. In light of the foregoing, it is unarguable that the present invention went against what was known in the art at the time of the invention by using a disintegration test to correlate the *in vitro* and *in vivo* active agent release profiles of the claimed controlled release dosage form. *See, Kloster Speedsteel AB v. Crucible, Inc., supra.*

With respect to the superiority of the unexpected superiority of the disintegration test for predicting *in vivo* drug release, applicants direct the Examiner's attention to Example 1, and Figures 1 and 2, of the specification, which clearly shows that the disintegration test has a closer correlation to the *in vivo* drug release profiles of the claimed controlled release dosage forms than does the dissolution test.

Because the claimed invention is not rendered obvious by the combination of Shell et al. in view of the teachings in the specification, applicants respectfully request withdrawal of this rejection.

THE UNITY OF INVENTION OF CLAIMS 1 AND 17

At the bottom of page 4 of the Office Action, the Examiner requests a discussion on why the subject matter of the two claims should not be restricted.

The method of claim 1 relates to a method for selecting an optimized controlled release dosage form for administration to a patient such that the dosage form will have a predetermined drug release profile *in vivo*, the method comprising (a) preparing a plurality of different candidate dosage forms each comprised of a biocompatible, hydrophilic polymer and a pharmacologically active agent incorporated therein; (b) obtaining the *in vitro* drug release profile for each candidate dosage form in an aqueous medium in a USP disintegration tester; (c) comparing the *in vitro* drug release profiles obtained in (b), and determining which of the *in vitro* drug release profiles correlates most closely with a desired *in vivo* drug release profile; and (d) selecting the dosage form having the determined *in vitro* drug release profile for administration to a patient.

The method of claim 17 relates to a method for delivering a pharmacologically active agent to the upper gastrointestinal tract of a patient over an extended period of time while minimizing delivery to the lower gastrointestinal tract and colon, the method comprising orally administering to a patient in whom

the fed mode has been induced a sustained release oral dosage form comprised of a therapeutically effective amount of the pharmacologically active agent incorporated in a matrix of at least one biocompatible, hydrophilic polymer that (a) swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide gastric retention of the dosage form in the stomach of a patient in whom the fed mode has been induced; (b) gradually erodes within the gastrointestinal tract over a determinable time period; and (c) releases the active agent throughout the determinable time period, wherein the dosage form is optimized by subjecting the dosage form to a disintegration test for an extended period of time such that the dosage form has an *in vitro* active agent release profile that correlates to a desired *in vivo* active agent release profile for the dosage form.

As noted by the Examiner, claim 1 recites a method of selecting an optimized dosage form and claim 17 recites a method of delivering a pharmacologically active agent to the upper GI tract. The claims should not be restricted because they both recite a dosage form comprised of a biocompatible, hydrophilic polymer and a pharmacologically active agent that is optimized by subjecting the dosage form to a disintegration test such that the dosage form has an *in vitro* active agent release profile that correlates to a desired *in vivo* active agent release profile; accordingly, a search into the patentability of either of the claims would require a search for these important elements. Indeed, the rejections in the Office Action under reply appear to indicate that the Examiner did in fact already conduct such a search.

Because the Examiner appears to have already conducted a thorough search on the invention as recited in claims 1 and 17, restriction in this case would not be proper because such a restriction would not be in anticipation of a serious burden on the Examiner in the search and examination of the claimed invention. *See*, MPEP § 803 (If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.).

THE PROVISIONAL DOUBLE-PATENTING REJECTION

Claims 1-3 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 49-51 of copending U.S. Patent Application Serial No. 10/281,284 and claims 1-3 and 25 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 47-49 of copending U.S. Patent Application Serial No. 10/293,217.

Applicants acknowledge the Examiner's provisional double-patenting rejections and will amend and/or cancel the conflicting claims from the two sister cases identified in the Office Action. Because the two sister applications have not yet been examined, applicants respectfully request reversal of the instant provisional double-patenting rejection from this application, which is currently under examination, and

the reinstatement of the rejections in the corresponding sister applications, which have no yet come under examination.
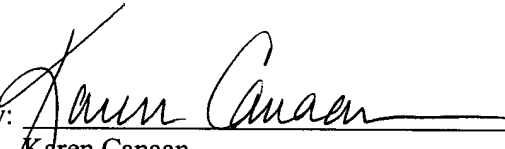
THE PRIOR ART NOT OF RECORD

Applicants have reviewed the prior art made of record and not relied upon and agree with the Examiner that the subject matter of the prior art has no bearing on the patentability of the claimed invention.

CONCLUSION

The foregoing discussion addresses all issues set forth in the Office Action and overcomes the anticipation and obviousness rejections set forth therein. Because there will be no outstanding issues for this application upon entry of this paper, applicants respectfully request reversal of all outstanding rejections for this application and passage of this application to allowance.

If the Examiner has any questions regarding this Amendment that may be addressed by way of a telephone call or e-mail correspondence, she is encouraged to contact the undersigned at 650-251-7713 or canaan@reedpatent.com.

Respectfully submitted,

By: _____
Karen Canaan
Registration No. 42,382

REED IP LAW GROUP
1400 Page Mill Road
Palo Alto, California 94304-1124
(650) 251-7700 Telephone
(650) 251-7739 Facsimile

CHAPTER 15

Introduction to
Rate of Dissolution
in Vitro and in Vivo

Introduction

DISSOLUTION IS THE ACT OF DISSOLVING. RATE OF DISSOLU-
tion is the rate of dissolving of a chemical or medicament
from the solid state. In biopharmaceutics rate of dissolu-
tion usually refers to the rate of dissolving of the medica-
ment from an intact dosage form or from fragments or
particles formed from the dosage form during the test.
Rate of solution and *rate of dissolution* may be used
interchangeably as was done by Hixson and Crowell
(1931). Although the first article cited* (Noyes and
Whitney, 1897) employed *rate of solution* in its title,
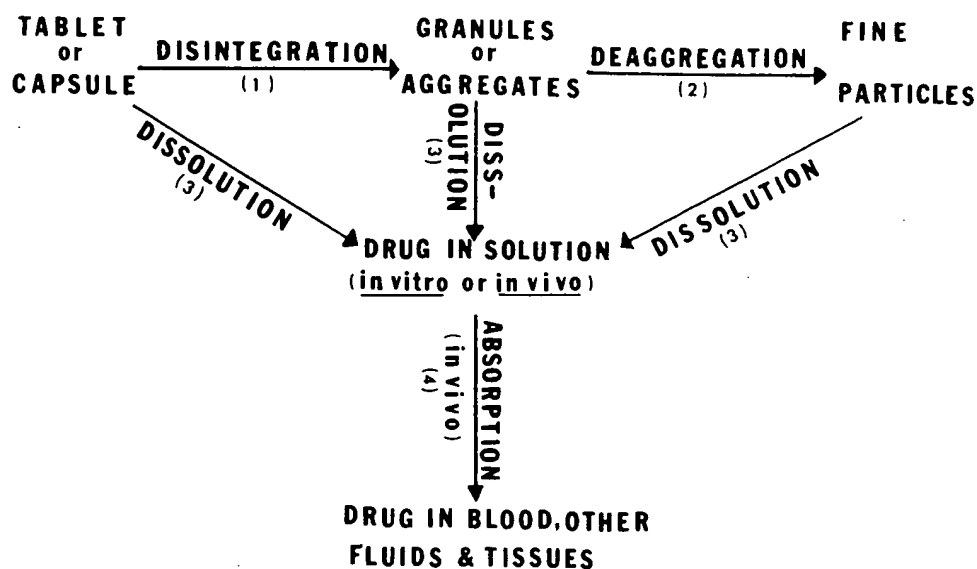most current authors appear to prefer *rate of dissolution*
or *dissolution rate*.

Scheme 15.1 indicates the processes involved when a
tablet or capsule is exposed to fluid under suitable con-
ditions *in vitro* or in the gastrointestinal contents *in vivo*
after oral administration. Dissolution of the drug occurs
not only from the fine particles of the drug ultimately
produced but also to a small degree from the intact
dosage form before its disintegration and from the frag-
ments and agglomerates produced after disintegration.
Dissolution occurs simultaneously from several types
of solid as the scheme indicates. In most *in vitro* test
systems nothing analogous to process 4 is included.

However in some *in vitro* test systems there is another
compartment which, in a sense, simulates "drug in blood,
other fluid and tissues." For example, in the dialysis
method (Barzilay and Hersey, 1968) a dialyzing mem-
brane is employed. One may also perform simultaneous
dissolution and partitioning studies *in vitro* (Niebergall
et al. 1967) in which case the drug dissolved in an
aqueous phase during a test is transferred to an organic
solvent immiscible with the aqueous phase. *In vivo*, as
the scheme indicates, process 4 involves absorption of
the drugs. The drug dissolved in the gastrointestinal
contents must diffuse in the aqueous fluids to the
gastrointestinal barrier and then be transported through
the barrier to the circulation. For most drugs absorption
involves adsorption and/or simple partitioning followed
by diffusion in the lipoid barrier. In a few cases an
active transport process or a different specialized process
may be involved.

Dissolution Rate-Limited Absorption

As indicated formerly, there is adequate evidence to
conclude that the rate at which a drug dissolves from its

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*Citations refer to the chronological bibliography, page 133.

TABLET or CAPSULE → DISINTEGRATION (1) → GRANULES or AGGREGATES → DEAGGREGATION (2) → FINE PARTICLES

TABLET or CAPSULE → DISSOLUTION (3) → DRUG IN SOLUTION (in vitro or in vivo)

GRANULES or AGGREGATES → DISSOLUTION (3) → DRUG IN SOLUTION

FINE PARTICLES → DISSOLUTION (3) → DRUG IN SOLUTION

DRUG IN SOLUTION (in vitro or in vivo) → ABSORPTION (in vivo) (4) → DRUG IN BLOOD, OTHER FLUIDS & TISSUES

Scheme 15.1

intact or fragmented dosage forms in the human gastrointestinal tract, or in a parenteral injection site, often partially or completely controls the rate at which the drug appears in blood (*i.e.*, the rate of absorption). There is also adequate evidence to conclude that in many cases *in vitro* rate of dissolution test results can be used to *explain* observed differences in results obtained in animals and human subjects or patients. When the dissolution process (process 3 of Scheme 15.1) is very much slower (*e.g.*, less than 1/20 the rate) than the disintegration process (process 1), the deaggregation process (process 2) and the absorption process (process 4) then dissolution essentially completely controls absorption rate. There may be many cases when two or more of the processes proceed at a rate within a factor

of 20 of each other in which cases rate of dissolution would only partially control absorption rate. It should be noted, however, that the rates of the processes of disintegration, deaggregation and dissolution are all dependent upon the composition and method of preparation of the dosage form. These rates are all largely dependent upon *pharmaceutical* factors which the formulator can alter. The reasons for measuring disintegration times and rates of dissolution were presented formerly* and should be reviewed at this time.

Historical Highlights

In 1897 Noyes and Whitney published their law which concerns the rate at which solids dissolve in their own

solutions. The law resulted from experiments in which they measured the amount of substance (benzoic acid and lead chloride) dissolved at different times when constant surface cylindrical sticks of the substance were rotated in water. They explained the dissolution process on the assumption that a very thin layer of saturated solution was formed at the surface of the solid and that the rate at which the solid dissolved was governed by the rate of diffusion from this saturated layer into the main body of the solution.

Brunner and Tolloczko (1900, 1901, 1903) showed that the proportionality constant relating the rate of change of concentration to the concentration difference in the Noyes-Whitney equation (1897) depended upon the surface area of the exposed solid, the intensity of agitation or velocity of fluid flowing across the solid, the temperature, the structure of the surface and the experimental apparatus.

Nernst and Brunner (1904) advanced a theoretical generalization of the Noyes-Whitney law to include all kinds of heterogeneous reactions. They postulated that the velocity of a heterogeneous reaction was determined by the velocities of the diffusion processes that accompanied it. This included the concept that the solute-solution equilibrium is set up at the boundary surface practically instantaneously compared with the rate of diffusion. They used Fick's law of diffusion to establish a relationship between the proportionality constant involved and the diffusion coefficient of the solute. In this way they were able to estimate the thickness of the film or diffusion layer at the surface of the solid.

Over the years there have been several critics of the Nernst-Brunner (1904) theory; one of these was Wilderman (1909); Wurster and Taylor (1965) in their review refer to others. However, in general, with some modifications the theory has withstood the test of time.

In 1931 Hixson and Crowell wrote an excellent review of the theory of the dissolution of solids and derived their "cube root law" in which the velocity of solution of a solid in a liquid is expressed as a function of the surface area and the concentration. The derivation of their "cube root law" is based on the following assumptions: (1) dissolution takes place normal to the surface of the dissolving solid; (2) the same effect of agitation is observed on all areas of the surface; (3) no stagnation of the liquid takes place in any region; and (4) the solid particle remains intact through the dissolution process.

In 1932 Klein was the first investigator to determine the rate of dissolution of a compressed tablet. A year later, Elliott (1933), using Klein's apparatus which Elliott called a Solvometer, published plots of amounts of drug dissolved against time following tests on compressed tablets of five different drugs. He attempted "to show the influence exerted upon the rate of solution by two important variables—temperature and surface in contact with the liquid." Elliott's tablets apparently had essentially constant surface areas during dissolution since he found that the rates of solution were essentially con-

*See Chapter 10, page 64.

stant until about nine-tenths of the tablets was dissolved.

King and Brodie (1937) studied dissolution of rotating cylinders of benzoic acid in water and in sodium hydroxide and potassium hydroxide solutions. They explained their data on the basis of the Nernst-Brunner film theory which assumes linear concentration gradients of all species in the diffusion layer. Later, W. I. Higuchi et al. (1958) showed where the assumption of linear concentration gradients would fail.

In 1938 Marshall et al. clearly showed the dose dependence of blood levels of sulfanilamide and acetylsulfanilamide in dogs. They stated, "Acetyl-sulfanilamide is much less soluble in water than sulfanilamide and might be expected to be absorbed less readily and completely than sulfanilamide." They showed that increasing the dose of sulfanilamide from 0.16 Gm/Kg to 1.6 Gm/Kg caused an approximate tenfold increase in peak blood level of sulfanilamide; however, increasing the dose of the less soluble acetylsulfanilamide from 0.16 Gm/Kg to 1.6 Gm/Kg caused very little increase in the peak blood level. The concept of a relatively fixed time for drug at the absorption sites and relative rates of dissolution (which in turn are related to the solubilities) readily explain such data.

Oser, Melnick and Hochberg (1945) employed urinary excretion data in proposing the concept of physiological availability of the vitamins from pharmaceutical products. They demonstrated clearly that within certain limits a direct relationship exists in normal subjects between the urinary excretion of water-soluble vitamins and the amount ingested. This relationship provided a means to assess physiological availability of the vitamins in pharmaceutical products by measurement of urinary excretion of the vitamins in man after ingestion of products intended for oral administration. Such data have been used in biopharmaceutics to correlate with in vitro data such as disintegration time and rate of dissolution.

In 1951 Danckwerts introduced another model for dissolution where one imagines macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in some random fashion. During its residence at the interface the packet is able to absorb solute according to the usual laws of diffusion. These surface elements are continuously replaced by new packets of solvent. This surface renewal process may then be related to the solute transport rate.

In the same year, Edwards (1951) predicted that "for aspirin in tablet form the rate controlling process, as far as analgetic action in the blood is concerned, is the dissolution within the stomach and intestine." This prediction was based on the in vitro rate of dissolution of aspirin as a function of pH, the rate of diffusion of aspirin in aqueous solutions, and theoretical calculations. However, he did not test his hypothesis in vivo nor did he seem to be aware of the earlier work of Marshall et al. (1938) and Oser et al. (1945).

In 1953 Smith, Kline and French Laboratories marketed the first "sustained-release" Spansule product. Subsequently, a host of prolonged action and sustained-release products have been marketed. The results achieved

with these products are directly related to slower absorption of the contained drugs relative to conventional dosage forms. Indirectly, the slower absorption is attributable to slower dissolution of the drug from the dosage forms in the gastrointestinal tract of man.

Nelson (1957) showed there were marked differences in the intrinsic *in vitro* rates of dissolution of theophylline salts and hypothesized that these differences could explain differences in peak blood levels and prolongation of blood levels observed by other workers when these salts were administered orally to human subjects. Nelson stated, "Other factors remaining constant, solution rate determines blood level and rate of build-up of blood level with time."

In the same year, Brodie and Hogben (1957) ascribed the long duration of action of the centrally acting muscle relaxant, zoxazolamine, to precipitation of the drug in the intestines where, due to its low solubility, it dissolves slowly and is absorbed slowly during many hours after oral administration.

In 1958 W. I. Higuchi and associates examined the problem of dissolution rates of solids in reactive solutions by the simultaneous chemical reaction and diffusion (SCRD) method. This was an experimental and theoretical study of the influence of bases and buffers on rates of dissolution of acidic solids. The SCRD method employed the Nernst-Brunner model and assumed nonlinear concentrative gradients in a single diffusion layer. They showed that complex rate equation which they derived could be reduced to more simple equations under certain conditions which may be readily determined by a consideration of the dissociation constants of the acids and bases involved in a particular system.

Nelson (1959) and Nelson and Schaldemose (1959) discussed solution rate-limited and non-solution rate-limited absorption and pointed out the value of urinary excretion kinetics for evaluation of rate of drug absorption.

Shenoy, Chapman and Campbell (1959) published data on the urinary excretion rates and physiological availability measured in man, and *in vitro* rates of release from eight different pelleted products of amphetamine labeled as being of the sustained-release type. Only two of the eight preparations tested demonstrated constant urinary excretion at an adequate level and were quantitatively available. They stated, "The data suggest that marked diferences may be expected in the clinical effect of 'sustained-release' products presently on the market."

Simultaneously, in the same journal, Wiegand and Taylor (1959) and Wagner (1959) published papers indicating that many sets of percent released-time data, previously published and based on *in vitro* tests of prolonged action and sustained release preparations, could be adequately described by apparent first order kinetics.

In 1960, Levy and Hayes discussed the physicochemical basis of the buffered acetylsalicylic acid controversy. They concluded that the incidence of local irritation and the absorption rate of acetylsalicylic acid is a function of its dissolution rate in its particular dosage form. They described a dissolution assembly, later to become known as the "beaker method," which provided mild agitation conditions for determination of dissolution rates of tablets.

Wagner, Carpenter and Collins (1960) compared plasma 17-OHCS levels in the dog following oral administration of compressed tablets and pH-dependent coated granules containing prednisolone. They also compared plasma 17-OHCS levels in man following oral administration of compressed tablets, pH-dependent coated granules and pH-independent coated granules containing prednisolone in man. *In vitro* release rates as a function of pH were also presented. These data clearly show one must be very careful about extrapolating *in vitro* data to man. Although the pH-dependent and pH-independent granules released drug entirely different *in vitro*, the plasma 17-OHCS levels measured over a 24-hour period following administration to man were essentially equivalent. Both granules forms provided prolonged plasma 17-OHCS levels compared with those achieved with the tablet.

Stone (1960) filed a patent to cover a method of solubilizing relatively insoluble antibiotics. The method involved dissolving the antibiotic and a highly soluble polymeric material such as polyvinylpyrrolidone (and other specified polymers) in a mutual essentially non-aqueous solvent and then removing substantially all the solvent to obtain a readily soluble residue. Later, Simonelli, Mehta and Higuchi (1968) showed that drugs so treated with PVP were essentially amorphous in nature and this accounted for the high dissolution rates of the drugs so treated.

In 1961 Levy correlated dissolution and absorption rates of different commercial aspirin tablets and proved that Edwards' (1951) hypothesis was correct.

The review entitled "Biopharmaceutics: Absorption Aspects" (Wagner, 1961) established biopharmaceutics as a new subject. This review clearly established the role of dissolution rate studies in this new field.

In the same year, at a Teachers' Seminar in Pharmacy, T. Higuchi (1961) discussed the role of crystal structure on availability and stability of some pharmaceuticals. This led to much subsequent research on use of different polymorphic forms and solvates to improve dissolution characteristics of drugs.

In the same year, Sekiguchi and Obi (1961) developed a new technique to achieve particle size reduction of a drug and thereby permit sparingly soluble drugs to become dispersed finely in the fluids of the gastrointestinal tract. The method involves the formation of a eutectic mixture of the drug (solid at room temperature) and a pharmaceutically inert, readily soluble carrier. Sulfathiazole in a eutectic mixture with urea exhibited higher absorption and urinary excretion in man than ordinary sulfathiazole after oral administration. Later, Sekiguchi *et al.* (1964) studied the chloramphenicol-urea system. Still later, Goldberg, Gibaldi and Kanig (1965) summarized literature on eutectic mixtures and solid solutions and studied the acetaminophen-urea system (1966), the griseofulvin-succinic acid system (1966) and the chloramphenicol-urea system (1966).

In 1962, Hamlin, Nelson, Ballard and Wagner showed that increasing the intensity of agitation in dissolution

rate studies on two polymorphic forms of methylprednisolone resulted in a loss of sensitivity and a failure to distinguish between the polymorphs with respect to dissolution rate. This study emphasized the need for low intensities of agitation in many *in vitro* dissolution rate tests. Levy and Procknall (1964) studied the same polymorphs by the rotating disk method and confirmed that the observations of Hamlin *et al.* (1962) were due to the intrinsic properties of the drugs and not to the particular apparatus employed. They stated, "It is certainly appropriate to characterize the dissolution rate dependence of drugs on agitation intensity aspect of their biopharmaceutical evaluation." The observations of Hamlin *et al.* (1962) were explained on the basis of the Danckwerts' model by Goyan (1965) and on the basis of a double barrier model by Wurster and Taylor (1965). However, the most plausible explanation of the observation's of Hamlin *et al.* (1962) was given by W. I. Higuchi *et al.* (1967).

Schroeter, Tingstad, Knoechel and Wagner (1962) reported that with some tablets there was a quantitative relationship between rate of dissolution (as reflected by the $t_{50\%}$ values) and disintegration time but with other tablets there was no such relationship. Where a quantitative relationship existed, the slopes of the lines relating the variables varied widely and depended upon the particular drug involved and, in one case, upon the presence and absence of sodium chloride as an ingredient in the tablets. These authors questioned the use of plastic disks in the official tablet disintegration test. They also reevaluated the data of Chapman *et al.* (1956) and showed that physiological availability of p-aminosalicylate was correlated with dissolution rate as well as with disintegration time.

Levich (1962) showed that the hydrodynamics associated with the rotating disks method for determination of rates of dissolution are such that the diffusion layer model *per se* is not applicable and that the so-called "Levique equation" must be used to interpret data obtained by this method.

Schroeter and Wagner (1962) described the first automated dissolution rate apparatus. A modification of this apparatus was reported later by Schroeter and Hamlin (1963). Other automated apparatus for dissolution rate studies were described by Niebergall and Goyan (1963), Pernarowski *et al.* (1968), McClintock *et al.* (1968) and Barzilay and Hersey (1968).

W. I. Higuchi and Hiestand (1963) derived an equation to describe the dissolution rate of a particle with time in a diffusion-controlled process then applied the equation to a hypothetical powder whose particles are approximately log-normally distributed. For relatively large particles the change in volume with change in radius is small and may be disregarded; but for very small particles the change in volume with change in radius is large and must be taken into consideration. W. I. Higuchi, Rowe and Hiestand (1963) applied the equation to the dissolution rate of micronized methylprednisolone in aqueous solutions and reasonably good agreement between experiment and theory was obtained.

Shefter and T. Higuchi (1963) showed that the anhydrous and organic solvate forms of several drugs dissolved more rapidly than the corresponding hydrated forms. They derived equations relating the solubility products and diffusional constants to rates of solution of organic solvates. They pointed out that the formation of organic solvates of many highly insoluble drugs is a very useful method for effecting rapid dissolution of such drugs.

T. Higuchi (1963) derived equations which gave theoretically expected rates of release of solid drugs incorporated into solid matrices based on several model systems.

W. I. Higuchi, Nelson and Wagner (1964) demonstrated that within the framework of the diffusion layer model the total solubility method based on the Noyes-Whitney law (1897) and the SCRD method (W. I. Higuchi *et al.*, 1958) give the same results when all of the diffusion coefficients may be set equal to the same value. Because diffusion coefficients of solute molecules do not differ much in general and other uncertainties— such as variation of dissociation constants and solubilities with ionic strength and other solute interaction effects— are frequently overriding factors, it would be expected that the total solubility method should explain most experimental results as well as the SCRD method.

Goyan (1965) used Danckwerts' (1951) penetration model to derive equations for the dissolution of solids in a multiparticulate system. The equations obtained are capable of explaining the deviation from linearity of Hixson and Crowell (1931) type cube root plots.

W. I. Higuchi, Mir and Desai (1965) developed theory for the dissolution rate of polyphase mixtures based on the diffusion layer model. The theory explained the observation of Nelson (1958) that there was a maximum in the plot of dissolution rate *versus* composition for the benzoic acid-trisodium phosphate system. In the opinion of the writer the use of basic compounds with poorly soluble weakly organic acidic drugs is not utilized in tablets and capsules to nearly the extent that it should be. This article of W. I. Higuchi *et al.* (1965) clearly outlines the theory for such use.

Hamlin, Northam and Wagner (1965), using compressed pellets in a standard apparatus, showed that the initial rate of dissolution (sink conditions) was directly proportional to the solubility of the drug in the dissolution medium, in conformity with the Noyes-Whitney (1897) law for a large number of drugs of widely varying structures. This supported the conclusion of W. I. Higuchi, Nelson and Wagner (1964). Exceptions to such a relationship are self-coating pellets such as described by Levy and Procknall (1962) and Higuchi and Hamlin (1963).

Levy, Leonards and Procknall (1965) developed a method of correlating absorption data estimated from urinary excretion of salicylate following oral adminstration of aspirin to man with *in vitro* rate of dissolution data derived from the same dosage forms of aspirin.

In a series of important papers W. I. Higuchi and associates (Desai, Simonelli and Higuchi, 1965; Desai,

Singh, Simonelli and Higuchi, 1966; Singh, Desai, Simonelli and Higuchi, 1968; Schwartz, Simonelli and Higuchi, 1968) elucidated the role of a number of factors controlling the rate of drug release from a variety of plastic and wax matrices and developed and applied theoretical approaches to this area.

Knoechel, Sperry and Lintner (1967), using an instrumented rotary tablet process which they designed and instrumented, obtained much experimental data on the relationship between rate of dissolution and compressional force and other variables when compressed tablets are made under actual production conditions.

W. I. Higuchi, Bernardo and Mehta (1967) reported a correlation between the rates of reversion of the metastable forms to the stable forms during dissolution and the crystal growth rates of the stable form for two polymorphic forms of both sulfathiazole and methylprednisolone. The usefulness of a polymorphic form of a drug to increase rate of dissolution may be gauged not only from this paper but from the previous one of W. I. Higuchi, Lau, T. Higuchi and Shell (1963) and the papers of Wurster and Taylor (1965).

Niebergall, Patil and Sugita (1967) presented an *in vitro* method for the simultaneous determination of dissolution rate and partitioning into a water-immiscible solvent in contact with the dissolution medium. The kinetics of the system were found to be in agreement with expectations for diffusion controlled processes.

Finholt and Solvang (1968) compared the kinetics of *in vitro* dissolution of phenacetin and phenobarbital in powdered form in human gastric juice with those in dilute hydrochloric acid containing varying amounts of polysorbate 80. The effect of polysorbate 80 on the rate of dissolution of phenacetin was shown to be due only to a small extent to its solubilizing power; but the principal effect of the surfactant was to decrease the interfacial tension between the drug particles and the dissolution medium. They showed that the surface tension of the dissolution medium has an appreciable effect on the dissolution kinetics of the two drugs studied.

Aguiar *et al.* (1968) demonstrated that deaggregation of powder in capsules after disintegration of the capsule shell may be a most important factor in drug availability and rate of dissolution. Such deaggregation kinetics may explain, in large part, the marked differences in physiological availability of various brands of chloramphenicol capsules reported by Glazko *et al.* (1968).

Thomas and Armstead (1968) showed that under static conditions rate of dissolution was proportional to the 4/3rd power of solubility when the lower faces of large potassium chloride crystals dissolved in mixtures of ethanol and water. They illustrated a regular pattern of etch pits on the crystal faces due to convective stirring action.

Brice and Hammer (1969) measured oxytetracycline serum concentration in 16 two-way crossover studies in 20 subjects each study. A single lot of Pfizer oxytetracycline capsules was the control treatment in each of the studies. Sixteen lots of oxytetracycline from 13 different suppliers constituted the other treatments. In each study the Pfizer oxytetracycline capsules produced superior serum levels. Seven of the 16 lots from other suppliers produced serum levels which were generally below the usually accepted minimum therapeutic level of 0.6 μg/ml. In an attempt to explain the differences these authors performed various disintegration and dissolution tests. They found that, in general, lots which gave poor serum levels also had slower rates of dissolution *in vitro*. They stated, "However, it is apparent that predictions of therapeutic availability cannot be made with precision from *in vitro* experiments in this case."

Tingstad and Riegelman (1969) described a continuous flow apparatus for determination of rates of dissolution. Rather than the usual cumulative plot of percent dissolved *versus* time, this type of test produces a plot of instantaneous rate of dissolution *versus* time.

Wagner (1969) discussed the interpretation of percent dissolved-time data derived from conventional testing of tablets and capsules from which drug dissolves reasonably rapidly. It was shown why, when surface area decreases exponentially with time, after some lag time, one would expect the data to obey first order kinetics. A distribution function, such as the logarithmic-normal distribution or the logistic-logarithmic distribution, may better be utilized to linearize percent dissolved-time data.

Blythe (1969) discussed a systematic approach to bioavailability testing. He pointed out that in future years a great deal of effort will have to be expended to obtain the human data and the *in vitro* data necessary to solve the generic equivalence-inequivalence problem.

Many other papers of historical, research and student interest have, by necessity, been omitted from this summary of the history of rate of dissolution *in vitro* and *in vivo*. However, it is hoped that this summary will orient the reader to the literature on rate of dissolution and make the subsequent material to be presented more meaningful in terms of historical perspective.